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DAVID W. HIGHET, VP AND CHIEF IP COUNSEL
BECTON, DICKINSON AND COMPANY
1 BECTON DRIVE, MC 110
FRANKLIN LAKES, NJ 07417-1880

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 12/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,949	DAVIS ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06242002*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

This application claims the benefit of the filing date of provisional application 60/261,448 with a priority date of January 12, 2001.

Claims 1-24 are currently pending.

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-24 as they pertain to fluorescently labeled multimeric complex comprising MHC class I domain moieties, a method of labeling T cells and a kit comprising the complex, in the reply filed on June 13, 2005 is acknowledged. The traversal is on the ground(s) that the four groups do not constitute separate inventions but are different species of the same invention.

This argument is not found persuasive in regard to the separation of the MHC molecules of groups I & II versus the antibodies of Groups III & IV because MHC complexes and antibodies are different kinds of protein molecules that are produced by a different set of cells and exhibits a different functional interaction with antigens. Antibodies can bind directly to a surface antigen receptor on a T cell, while an MHC molecule can bind to the antigen receptor only when a peptide antigen is bound to the MHC molecule for presentation to a specific T cell. Accordingly, claim 10 was separated into different groups because the claim embraces patentably distinct molecules. T he claim broadly recites a "means for binding to a T lymphocyte according to the specificity of its antigen receptor." The "binding means" therefore reads upon an antibody specific for antigen receptors on CD4+ T cells or CD8+ T cells. The term further reads upon MHC molecules that are specific for the antigen receptors on T cells. the claim does not recite that the binding complex comprises MHC molecules, nor does the claim recite that the complex comprises antibody. Accordingly, as both types molecules are capable of binding to a T cell, both MHC and antibodies are embraced within the breadth of the claim.

The argument is further found not persuasive in regard to the separation of Groups I & II. MHC class I molecules are present on all cells, whereas MHC class II molecules are expressed only by professional antigen presenting cells. Furthermore, MHC class I and MHC class II present a different set of antigenic peptides to different subsets of T cells.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-24 are the subject of examination in the present Office Action ONLY TO THE EXTENT that they read upon MHC class I complexes.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Page 54, for example, has an embedded hyperlink a lines 22-23. Applicant should peruse the instant specification for additional occurrences of hyperlinks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 5 and 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is an improper multiple dependent claim. Claim 5 depends upon more that one claim at a time rather than being alternatively dependent upon a single claim. Further, the elements upon which claim 5 is dependent constitute materially different compounds that are not interchangeable with one another and would not be related to one another as equivalents in a Markush group. It is suggested that the 4 elements of claim 5 be recited independently of one another in separate claims.

Claims 7 and 8 recite the limitation "F," "S" and "P" in the body of the claim. There is insufficient antecedent basis for this limitation in the claim. Claims 7 and 8 earlier recite only the formulas $(F_1S_1)_n$ in claim 7 and $(F_1S_1P_1)_n$ in claim 8. There is no basis for reciting F, S, or P and the terms F_1, S_1, and P_1 are left undefined in the claims.

Claim 9 is ambiguous in reciting "means for fluorescing," "means for multimerizing" and "means that are capable of contributing." Claim 10 is similarly ambiguous in reciting "means for fluorescing," and "means binding." The term "means" can either be a noun or used to define another term. Each of the noted occurrences should be amended to recite --a means-- in order to clarify that the term "means" is being used as a noun.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-17 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al (Science [1996] 274:94-96; cited on form PTO-1449 filed June 24, 2002) in view of Cormack et al (Gene [1996] 173:33-38; cited on form PTO-1449 filed June 24, 2002).

Altman teaches a recombinant fusion protein comprising an MHC class I heavy chain and a multimerization domain consisting of a 15 amino acid substrate for BirA-dependent biotinylation (page 94, third column in particular)[claim 1]. Altman teaches creation of a nucleic acid molecule expressing the fusion protein, a vector comprising the nucleic acid and a host cell expressing the fusion protein (page 96, second column in particular)[claims 2-5]. Claim 24 is included because the 15 amino acid substrate for BirA-dependent biotinylation incorporates a flexible peptide spacer separating the biotinylation site from the MHC molecule.

Altman does not teach the incorporation of a GFP-like chromophore into the fusion protein.

Cormack teaches FACS-optimized mutants of the GFP protein that can be incorporated into expressed proteins comprising a 20 amino acid region surrounding the chromophore (amino acids 55-74 of GFP, comprising the chromophore site of amino acids 65-67) (Abstract and page 34 in particular). Cormack teaches that these GFP-like mutants are superior because they may be detectable in systems in which wild-type GFP fluorescence is not visible.

Altman teaches the association of the fusion proteins with beta-2-microglobulin and the multimerization of the MHC complexes by incubation with deglycosylated avidin (paragraph bridging pages 33-34 in particular) and incorporation with a peptide antigen (paragraph bridging columns 1-2 of page 95 in particular)[claims 6-10].

Altman teaches a method of detecting, enumerating and enriching T cells reactive with the multimeric complexes (Figs. 1-2 in particular) [claims 11-13, 16, 17].

Altman further teaches a method comprising additional staining of the T cells with fluorescently labeled antibodies for pan-T cell (CD62L) and activation (CD38) markers (Figure 3 in particular) [claims 14, 15].

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to incorporate the GFP-like mutants of Cormack into the fusion protein of Altman between the MHC class I alpha extracellular domain and the multimerization domain in order to make an intrinsically fluorescent fusion protein. One would have been motivated, with a reasonable expectation of success to combine the teachings because the mutants taught by Cormack comprise the fluorescent domain internal to the small 20 amino acid segment and it therefore would retain the ability to fold properly to fluoresce. The artisan would further be motivated to combine the references with a reasonable expectation of success by the knowledge that the construct will have a 1:1 ratio between the level of fluorescence and the number of MHC class I molecules detected in an assay. The artisan would find this valuable for retaining correlation not only between samples within an assay, but also between assays because the level of fluorescence can vary between preparations of phycoerythrin labeled avidin molecules.

5. Claims 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al (Science [1996] 274:94-96; cited on form PTO-1449 filed June 24, 2002) in view of Cormack et al (Gene [1996] 173:33-38; cited on form PTO-1449 filed June 24, 2002) as applied to claims 1, 7 and 8 above, and further in view of U.S. Patent No. 6,232,445 to Rhode et al (A on form PTO-892).

Altman and Cormack have been discussed supra.

The combined references do not specifically teach gathering the components together in a kit form.

The '445 patent teaches that recombinant MHC molecules can be incorporated "as one component of a kit suitable for medical, research, home or commercial use" (column 10, lines 16-29 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to prepare the reagents prior to performing an assay and storing them as separate compositions in a kit form. The artisan would have been motivated to create such a kit with a reasonable

expectation of success by the knowledge that such a prepackaged kit would expedite the handling of samples when received from a clinical setting.

6. Claim 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altman et al (Science [1996] 274:94-96; cited on form PTO-1449 filed June 24, 2002) in view of Cormack et al (Gene [1996] 173:33-38; cited on form PTO-1449 filed June 24, 2002) and U.S. Patent No. 6,232,445 to Rhode et al (A on form PTO-892) as applied to claims 18 and 21 above, and further in view of U.S. Patent No. 4,902,613 to Chang et al (B on form PTO-892).

Altman, Cormack and the '445 patent have been discussed supra.

The combined references do not teach the inclusion of a red blood cell lysing agent in a kit.

The '613 patent teaches that approximately 90% of the cells in peripheral blood are red blood cells while lymphocytes make up the minor percentage of about 10% (column 1 in particular). The '613 patent teaches that this lysis of the red blood cells allows clean identification of different types of lymphocytes by means of flow cytometry (column 3, lines 36-64 in particular). the '613 patent teaches an agent that selectively lyses the red blood cells, leaving the lymphocytes intact (column 3, line 65 through column 4, line 62 in particular).

Altman teaches the analysis of cell staining by means of flow cytometry, but is silent about the use of a red blood cell lysing agent. Cormack teaches that the GFP-like mutants are optimized for use in flow cytometry.

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to include the red blood cell lysing agent of the '613 patent in a kit for the analysis of MHC multimer binding to target T cells. the artisan would have been motivated to ad the reagent to a kit with a reasonable expectation of success by the knowledge that the assay is searching for a subset of cells which comprise only a small portion of the minor population of cells obtainable from a peripheral blood sample. Accordingly, elimination of 90% of the cells from the sample, cells that are irrelevant to the assay anyway, would increase the sensitivity of the assay for the target cells.

Conclusion

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

F. Pierre VanderVegt, Ph.D.
Patent Examiner
November 25, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600